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DRUG INTERACTIONS

Evaluation of modafinil as a perpetrator of metabolic drug–drug interactions using a model informed cocktail reaction phenotyping trial protocol

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Keywords cytochrome P450, drug interaction

AIM

To evaluate the capacity for modafinil to be a perpetrator of metabolic drug–drug interactions by altering cytochrome P450 activity following a single dose and dosing to steady state.

METHODS

A single centre, open label, single sequence cocktail drug interaction trial. On days 0, 2 and 8 participants were administered an oral drug cocktail comprising 100 mg caffeine, 30 mg dextromethorphan, 25 mg losartan, 1 mg midazolam and 20 mg enteric-coated omeprazole. Timed blood samples were collected prior to and for up to 6 h post cocktail dosing. Between days 2 and 8 participants orally self-administered 200 mg modafinil each morning.

RESULTS

Following a single 200 mg dose of modafinil mean (± 95% CI) AUC ratios for caffeine, dextromethorphan, losartan, midazolam and omeprazole were 0.95 (± 0.08), 1.01 (± 0.35), 0.97 (± 0.10), 0.98 (± 0.10) and 1.36 (± 0.06), respectively. Following dosing of modafinil to steady state (200 mg for 7 days), AUC ratios for caffeine, dextromethorphan, losartan, midazolam and omeprazole were 0.90 (± 0.16), 0.79 (± 0.09), 0.98 (± 0.11), 0.66 (± 0.12) and 1.90 (± 0.53), respectively.

CONCLUSIONS

These data support consideration of the risk of clinically relevant metabolic drug–drug interactions perpetrated by modafinil when this drug is co-administered with drugs that are primarily cleared by CYP2C19 (single modafinil dose or steady state modafinil dosing) or CYP3A4 (steady state modafinil dosing only) catalysed metabolic pathways.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Modafinil is a vigilance promoting drug that is increasingly used for off-label and recreational indications with sporadic dosing patterns.
- Modafinil induces the *in vitro* expression of CYP1A2 and CYP3A4/5, and inhibits CYP2C9, CYP2C19 and CYP3A4/5 activities in a reversible, competitive manner.
- Steady state dosing of modafinil (200 mg daily for 4 weeks) reduces exposure to CYP3A4 substrates.

WHAT THIS STUDY ADDS

- Direct elucidation of the impact of single dose and steady state dosing of modafinil on a panel of the most important cytochrome P450 enzymes in terms of drug metabolism.
- Direct confirmation that sporadic recreational dosing of modafinil in young females is unlikely to reduce exposure to the contraceptive pill or increase the risk of unplanned pregnancy.
- Characterization of the capacity for modafinil to be a perpetrator of clinically important metabolic drug–drug interactions when co-administered with drugs metabolized by CYP2C19.

Introduction

Modafinil is a eugeroic drug approved by regulatory agencies in many countries for the treatment of narcolepsy and associated sleep disorders. This drug is also routinely used off-label as an adjunct treatment for depression and recreationally for its vigilance promoting and cognitive enhancing properties. The capacity of modafinil to be a 'perpetrator' of metabolic drug–drug interactions (mDDIs) by altering **cytochrome P450** (CYP) activity has been evaluated *in vitro*; modafinil induces the *in vitro* expression of CYP1A2 and CYP3A4/5 mRNAs, and inhibits the activity of CYP2C9, CYP2C19 and CYP3A4/5 in a reversible, competitive manner [1]. Dynamic extrapolation of these data using physiological-based pharmacokinetic (PBPK) modelling [2] indicate that modafinil may be a perpetrator of clinically relevant mDDIs when co-administered with drugs metabolized by CYP2C19 and CYP3A4. Modafinil is currently classified by the US Food and Drug Administration (FDA) as a 'moderate' CYP3A4 inducer. While *in vitro* data suggest a potential clinically relevant inhibition of CYP2C19, in the absence of clinical evidence to substantiate classification, the potential for modafinil to be a perpetrator of mDDIs by altering CYP2C19 activity remains unclassified. Given the major role of CYP in the metabolic clearance of drugs from various therapeutic classes as well as dietary, environmental and endogenous compounds [3], clarification of the capacity for modafinil to alter CYP activity *in vivo* is warranted.

To date, clinical studies assessing the capacity of modafinil to be a perpetrator of mDDIs have focused on a limited number of direct interactions based on the potential for concomitant use with other vigilance promoting (dexamphetamine, methylphenidate) and sedative (triazolam) medications [4–7]. Notably, in all cases the study 'victim' drugs were substrates for multiple (CYP and non-CYP) metabolic clearance pathways, and as such these studies do not facilitate an assessment of the impact of modafinil on individual CYP activities. A single clinical study has considered the capacity of modafinil to induce CYP enzymes [8]. This study, which used antipyrine as a pan-CYP substrate with 7 days of modafinil dosing, demonstrated a modest increase in total CYP expression at modafinil doses above 400 mg (double the standard dose). However, the study design did not facilitate assessment of induction of individual CYP or account for concurrent inhibition of these enzymes.

When considering the risk of mDDIs involving modafinil, it is important to consider that in addition to the limited approved indications for this drug, modafinil is increasingly used for a number of off-label indications [9] and recreational purposes [10]. In these less controlled settings, the drug may be dosed regularly or sporadically. As such, when evaluating the capacity of modafinil to be a perpetrator of mDDIs, it is important to do so in a manner that facilitates an understanding of the implications of different usage patterns.

In the current study, we assessed the impact of modafinil on individual CYP activities using an *in vivo* cocktail pathway phenotyping (ICPP) approach incorporating selective probes for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 [11]. A protocol that facilitated assessment of the impact of different modafinil usage patterns (single dose and steady state dosing) on CYP activity was optimized and validated prior to the commencement of this study using a PBPK modelling approach [2].

Methods

Study participants

Healthy males and females aged 21–40 years old were screened by physical examination and history. Participants were required to refrain from use of drugs and herbal products, including tobacco and alcohol, grapefruit juice and consuming large amounts of cruciferous vegetables for 7 days prior to and during the study. Participants were also required to abstain from caffeine for 48 h prior to administration of the drug cocktail on study days 0, 2 and 8. Female participants were required to provide a negative pregnancy test at the time of study enrolment and use two forms of contraception for the duration of the study.

Study protocol

This was a single centre, open label, single sequence cocktail drug interaction study that utilized a pre-specified PBPK model informed design to determine required sample size and dosing protocols [2]. The study protocol was approved

by the Southern Adelaide Clinical Human Research Ethics Committee (SAHREC 206.14), and written informed consent was obtained from each participant. The study was prospectively registered as a phase 0 clinical drug trial with the Australian Therapeutic Goods Administration (CTN 2014/0777) and Australian New Zealand Clinical Trials Registry (ACTRN 12614000451606).

On days 0, 2 and 8 participants (n = 6) were administered an oral drug cocktail comprising 100 mg caffeine (No-Doz Awakeners, Key Pharmaceuticals, NSW, Australia), 30 mg dextromethorphan (15 ml of 2 mg ml^{-1} dextromethorphan syrup; Bisolvon Dry, Boehringer Ingelheim, NSW, Australia), 25 mg losartan (Cozaar, Merck Sharp & Dohme Australia, NSW, Australia), 1 mg midazolam (1 ml of 5 mg ml^{-1} midazolam for injection diluted in 4 ml saline; Pfizer Midazolam, Pfizer, NSW, Australia), and 20 mg enteric-coated omeprazole (Acimax, AstraZeneca, NSW, Australia). Timed blood samples were collected prior to and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 h post cocktail dosing. Within 1 h of sample collection, plasma was isolated from whole blood by centrifugation at 4000g for 5 min and stored at −20°C until analysis. Between Days 2 and 8 participants orally self-administered 200 mg modafinil (Modavigil, CSL Biotherapies, Vic, Australia) each morning. On Days 2 and 8, modafinil was administered 1 h prior to dosing of the oral drug cocktail. A modafinil plasma concentration was determined 45 min post-dose on Days 2 and 8 to monitor adherence and ensure that steady state had been achieved.

Sample preparation

One hundred microlitres of plasma samples were diluted in 300 µl of methanol containing 0.1% formic acid and 7.5 ng ml^{-1} d_6-midazolam (assay internal standard) then vortexed for 3 min using a MixMate® Vortex Mixer (Eppendorf, Sydney, Australia) to precipitate plasma proteins. Samples were then centrifuged at 16 000g for 5 min, and a 2.5 µl aliquot of the resultant supernatant fraction was analysed by ultra-performance liquid chromatography-mass spectrometry (UPLC-MS). Quality control (QC) and calibration standards (n = 6) were prepared by spiking known concentrations of authentic standards for each analyte (cocktail probe) into drug-free plasma over a relevant concentration range.

Sample analysis

Samples were analysed using a validated method [12]. Briefly, analytes were separated from the sample matrix by ultra-performance liquid chromatography (UPLC) performed on a Waters ACQUITY™ BEH C18 column (100 mm × 2.1 mm, 1.7 µm; Waters Corp., Milford, USA) using a Waters ACQUITY™ UPLC system. The column temperature was maintained at 40°C, while the sample compartment was maintained at 15°C. Analytes were separated by linear gradient elution at a flow rate of 0.25 ml min^{-1}. Initial conditions were 70% water containing 0.1% formic acid (mobile phase A) and 30% acetonitrile containing 0.1% formic acid (mobile phase B). The proportion of mobile phase B was increased to 60% over 4 min, then returned to initial conditions.

Column elutant was monitored by mass spectrometry (MS), performed on a Waters Q-ToF Premier™ quadrupole, orthogonal acceleration time-of-flight tandem mass spectrometer (Q-ToF-MS) operating in positive electron spray ionization (ESI+) mode. The desolvation gas was set at a flow rate of 400 l h^{-1} at a temperature of 250°C, while the cone gas was set at a flow rate of 50 l h^{-1}. The source temperature was 90°C. Source capillary and cone voltages were 2.8 kV and 50 V, respectively. ToF data were collected in wide pass MS mode, with the resolving quadrupole acquiring data between m/z 150 and 600 to yield a total ion count (TIC) chromatogram. Data were collected as centroid spectra using the extended dynamic range function at an acquisition rate of 0.1 s, with a 0.05 s inter-scan delay. The collision cell energy was 2 eV. Selected ion data was extracted at the analyte [M + H] + precursor m/z. Resulting pseudo-MRM spectra were analysed using Waters TargetLynx™ software. Analyte concentrations in participant samples were determined by comparison of peak areas to those of calibrators. As reported previously [12], parameters defining assay precision, accuracy and sensitivity (lower limit of quantification; LLOQ) for each probe are reported in Table 1.

Data analysis

Non-compartmental methods (PK Functions for Microsoft Excel, Department of Pharmacokinetics and Drug Metabolism, Irvine, CA, USA) were used to estimate the area under the plasma-concentration–time curve to last sample (AUC), maximal concentration (C_{max}) and elimination

Table 1

Analytical assay performance

Drug	LLOQ (ng ml^{-1})	Precision at LLOQ (%CV)		Accuracy (% Dev)	Calibration range (ng ml^{-1})
		Intra-day	Inter-day		
Caffeine	25	7.6	9.7	11.2	25–2500
Dextromethorphan	0.08	8.4	11.8	9.5	0.1–75
Losartan	2.1	5.8	8.5	2.1	2.5–500
Midazolam	0.2	1.9	2.3	5.1	0.5–50
Omeprazole	3.5	1.9	3.4	12.1	5

half-life ($t_{1/2}$) for each probe in the absence of modafinil (Day 0), following a single modafinil dose (Day 2) and dosing of modafinil to steady state (Day 8). Probe AUC ratios in the absence and presence of modafinil (single dose and steady state) were assessed as the primary interaction outcome. The geometric mean of the AUC ratio was estimated using a mixed effects model of logarithmically transformed data. Time period was included as a fixed effect and participant as a random effect. Back transformation was utilized to provide a point estimate and 95% confidence interval (CI) for the AUC ratio.

Modafinil was judged to be a perpetrator of an mDDI for a given CYP if the 95% CI for the probe AUC ratio was not contained within the range 0.85–1.2 [13]. Based on the results of PBPK simulation [2], a sample size of six provided 87% power to discriminate such effects. The impact of modafinil on C_{max} and $t_{1/2}$ for each probe were assessed as secondary outcomes using the same approach.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [14], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [15].

Table 2

Participant demographics

	Mean (Range) or Count (%)
Age (years)	27 (24–34)
BMI (kg m^{-2})	21.8 (19.0–24.5)
Gender	
Male	4 (66.7%)
Female	2 (33.3%)
Ethnicity	
Caucasian	5 (83.3%)
Asian	1 (16.7%)

Results

Six participants (two females) completed the study (Table 2). No serious adverse events were reported by any participant; two of the six participants reported dry mouth, of those one also reported a modest reduction in mood and micrographia following modafinil administration. Adherence to modafinil was confirmed by assessment of plasma concentration on Days 2 and 8. Mean (± SD) modafinil plasma concentrations were 4.2 (± 0.6) and 5.8 (± 0.7) mg l^{-1} on Days 2 and 8, respectively. These concentrations are consistent with reported exposure for 200 mg modafinil following a single dose and 7 days dosing [16].

Baseline pharmacokinetic parameters (AUC, C_{max} and $t_{1/2}$) describing probe exposure were consistent with previous studies in healthy volunteers (Table 3) [11, 12]. Mean (95% CI) probe AUC, C_{max} and $t_{1/2}$ ratios compared to baseline following a single dose of modafinil (Day 2/Day 0) and 7 days of modafinil administration (Day 8/Day 0) are presented in Table 4. Changes in AUC and C_{max} are shown in Figures 1 and 2, respectively. Consistent with reported simulations [2], analysis of pre-dose samples on Day 2 and Day 8 demonstrated that in all cases residual baseline probe concentrations were below the assay lower limit of detection, thus supporting complete clearance of the prior probe doses on Days 0 and 2, respectively.

Pharmacokinetic parameters defining midazolam exposure were unaffected following a single modafinil dose; all parameters were within 10% of the baseline value. Dosing of modafinil to steady state resulted in a reduction in midazolam mean AUC from 9.7 to 6.4 μg l^{-1} h^{-1}. Consistent with the impact on AUC, steady state modafinil dosing caused a reduction in midazolam mean C_{max} from 7.7 to 5.6 μg l^{-1} and mean $t_{1/2}$ from 1.8 to 1.5 h (Table 4 and Figure 3). Following a single modafinil dose the mean AUC for omeprazole increased from 459 to 625 μg l^{-1} h^{-1}, while dosing of modafinil to steady state resulted in an increase in omeprazole mean AUC from 459 to 812 μg l^{-1} h^{-1} (Table 4 and Figure 4). As for midazolam, changes in omeprazole C_{max} and $t_{1/2}$ were consistent with the observed impacts on AUC (Table 4). All remaining pharmacokinetic parameters describing probe exposure were essentially unaffected by the presence of either a single modafinil dose or 7 days of modafinil administration (i.e. 95% CI for parameter ratio estimates were contained within the range 0.85–1.2).

Table 3

Baseline mean (± SD) pharmacokinetic parameters describing probe exposure in the absence of modafinil

Probe	Enzyme	AUC (μg l^{-1} h^{-1})	C_{max} (μg l^{-1})	$t_{1/2}$ (h)
Caffeine	CYP1A2	17 340 (± 3122)	1755 (± 148)	3.8 (± 0.5)
Dextromethorphan	CYP2D6	161 (± 40)	5.5 (± 1.5)	3.8 (± 0.7)
Losartan	CYP2C9	551 (± 52)	250 (± 72)	2.1 (± 0.5)
Midazolam	CYP3A4	9.7 (± 3.3)	7.7 (± 3.5)	1.8 (± 0.1)
Omeprazole	CYP2C19	459 (± 161)	456 (± 116)	0.7 (± 0.2)

Table 4

Mean (95% CI) probe AUC, C_{max} and $t_{1/2}$ ratios following a single modafinil dose (Day 2/Day 0) and 7 days of modafinil administration (Day 8/Day 0)

Probe	Enzyme	AUC Ratio		C_{max} Ratio		$t_{1/2}$ Ratio	
		Day 2/Day 0	Day 8/Day 0	Day 2/Day 0	Day 8/Day 0	Day 2/Day 0	Day 8/Day 0
Caffeine	CYP1A2	0.95 (0.87–1.03)	0.88 (0.73–1.07)	0.96 (0.79–1.14)	0.86 (0.68–1.05)	1.05 (0.98–1.13)	1.03 (0.97–1.10)
Dextromethorphan	CYP2D6	0.97 (0.71–1.33)	0.78 (0.69–0.88)	1.10 (0.70–1.50)	0.78 (0.67–0.89)	0.95 (0.87–1.04)	0.98 (0.92–1.04)
Losartan	CYP2C9	0.96 (0.86–1.07)	0.97 (0.88–1.08)	0.94 (0.86–1.02)	0.93 (0.89–0.98)	0.99 (0.92–1.05)	1.04 (0.92–1.16)
Midazolam	CYP3A4	0.97 (0.88–1.08)	0.65[a] (0.52–0.80)	0.90 (0.79–1.00)	0.73[a] (0.64–0.82)	0.89 (0.80–0.98)	0.81 (0.72–0.91)
Omeprazole	CYP2C19	1.36[a] (1.30–1.42)	1.85[a] (1.42–2.40)	1.22 (1.04–1.39)	1.54[a] (1.30–1.79)	1.77[a] (1.56–1.98)	2.04[a] (1.79–2.28)

[a]Parameter ratio consistent with an mDDI perpetrated by modafinil

Discussion

Here we report for the first time a systematic evaluation of the capacity of modafinil to be a perpetrator of mDDIs by altering activity for a panel of CYP enzymes following single dose and steady state dosing regimens.

Decreases in CYP activity are typically attributed to competition for binding at the enzyme active site, while increases in CYP activity are attributed to upregulation (induction) of CYP expression. Characterization of the capacity for time dependent (mechanism-based) inhibition of CYP activity by drugs from various therapeutic classes [17, 18] has had important clinical consequences for the way inhibition of this enzyme system is considered. In recent years, increasing structural insights regarding the CYP active site [19], along with mechanistic understanding of the kinetics of co-operative substrate binding [20, 21] have demonstrated the potential for non-induction-based activation of CYP activity. Indeed, multiple recent *in vitro* kinetic and mechanistic studies have demonstrated the capacity for significant (up to four-fold) increases in catalytic turnover due to enhanced alignment of substrate binding within the CYP active site, particularly for enzymes such as CYP3A4, which have a large active site volume [22–24]. Notably, to date, partially because interaction study protocols typically do not facilitate such assessment, no *in vivo* study has demonstrated non-induction-based activation.

Given the capacity of modafinil to both induce and inhibit CYP *in vitro*, including demonstrating both effects on CYP3A4, this drug was considered an ideal example to explore the potential clinical consequences of these different mechanisms of altered CYP activity. Given the indications for modafinil, this drug is typically administered to healthy individuals, thus minimizing the risk of typical DDIs resulting from polypharmacy. The increasing recreational use of modafinil for its vigilance promoting and cognitive enhancing actions does, however, represent a new range of DDI risks, the most prominent of these being the potential to reduce the efficacy of the contraceptive pill in young females by increasing CYP3A4 mediated oestrogen clearance [7]. Notably, prior characterization of the effect of modafinil on oestradiol clearance, which did demonstrate a potential interaction, considered only the impact of a steady state (4 weeks) modafinil dosing regimen, and did not provide insights regarding the potential consequences of sporadic (single dose) administration of this drug.

The limitation of this previous study becomes important when considering the potential clinical consequences and time course of the two plausible mechanisms of increased CYP3A4 activity. Firstly, where the increase in CYP3A4 activity is due to enhanced substrate binding, a single dose of modafinil may cause an immediate, but transient increase in oestrogen clearance that would resolve immediately following cessation of modafinil dosing. Similarly, with regular (steady state) modafinil dosing, the interaction would resolve upon complete removal of modafinil from the body, i.e. within 60 h based on the 12-h half-life of this drug [25]. The clinical consequence of this time course is that co-administration of modafinil with the contraceptive pill would place a female at increased risk of unplanned pregnancy following either a single dose of modafinil or

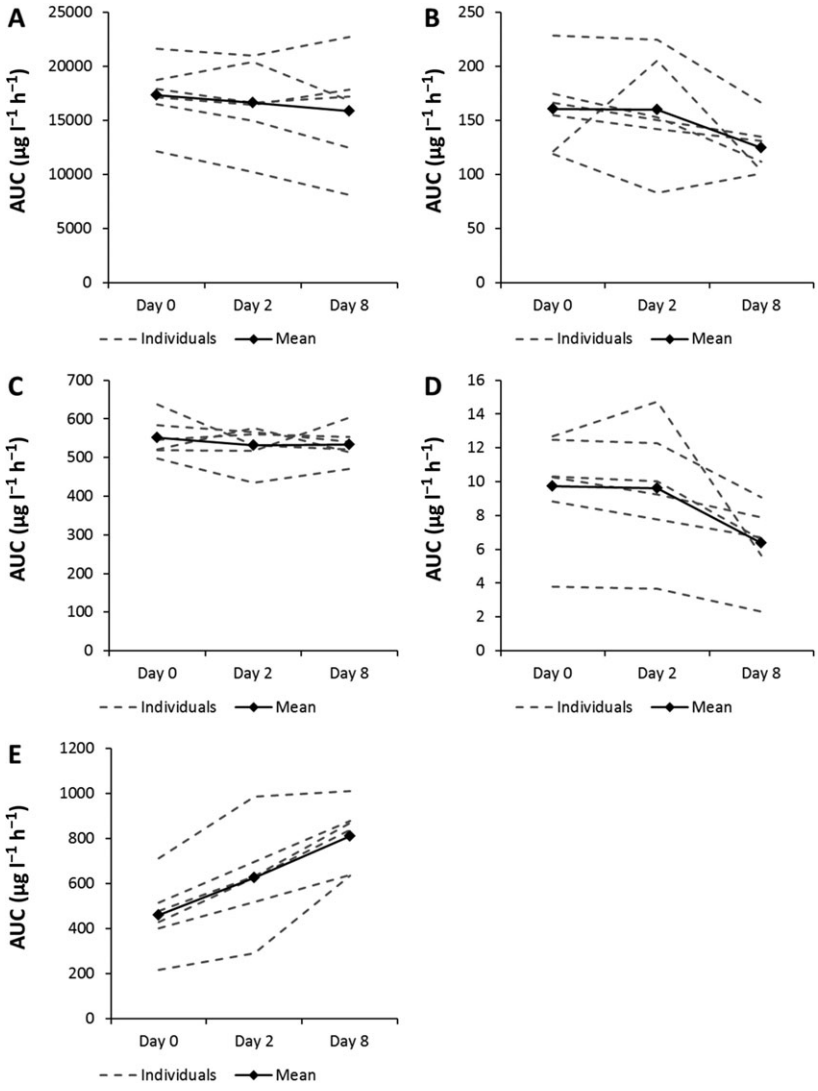

Figure 1

Spaghetti plot showing change in AUC from baseline (Day 0), following a single dose (Day 2) and dosing of modafinil to steady state (Day 8). Panel A: caffeine; Panel B: dextromethorphan; Panel C: losartan; Panel D: midazolam; Panel E: omeprazole. Dashed lines represent individual participant data, while the solid line represents the cohort mean

steady state modafinil dosing, but only for a limited time after ceasing modafinil even following regular dosing.

In contrast, where the increase in CYP3A4 activity is due to induction of CYP3A4 expression, a single dose of modafinil would be unlikely to increase CYP3A4-mediated oestrogen clearance to a significant extent, but the interaction would persist for a prolonged period upon complete removal of modafinil from the body. Indeed, we and others [26] have demonstrated previously that induction of CYP3A4 activity by alternate inducers persists for up to 3 weeks following cessation of the induction perpetrator. The clinical consequence of this time course is that co-administration of a single dose of modafinil with the contraceptive pill would be unlikely to place a female at increased risk of unplanned pregnancy. However, a female may be at increased risk of unplanned pregnancy for a prolonged time (based on the turnover of this enzyme [26] potentially up to 2 weeks) following cessation of steady state dosing of modafinil.

In the current study, a model-informed trial protocol was utilized to facilitate assessment of single dose and worst case steady state induction [2]. As reported previously, pre-specified PBPK modelling and simulation confirm that steady state exposure to modafinil is achieved within the 7-day perpetrator dosing period recommended by the FDA for the assessment of induction and mechanism-based inhibition mDDIs [27]. The use of a model-informed trial design further enabled the robust determination of a minimal sample size (n = 6) required to provide sufficient power to reject the null hypothesis. While routinely used in industry, model-informed trial designs are rarely used in investigator initiated trials, but provide substantial capacity to maximize the efficiency and value of such trials.

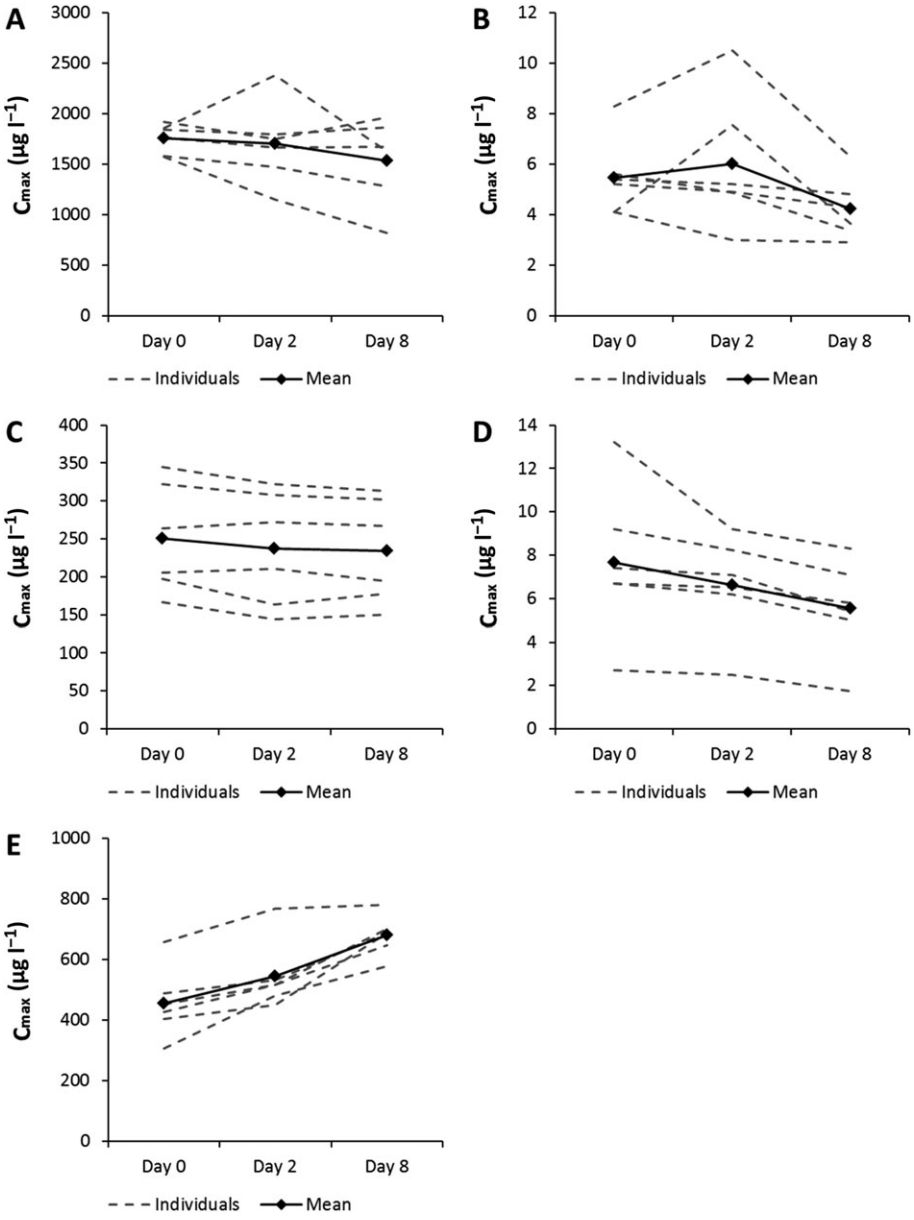

Figure 2

Spaghetti plot showing change in C_{max} from baseline (Day 0), following a single dose (Day 2) and dosing of modafinil to steady state (Day 8). Panel A: caffeine; Panel B: dextromethorphan; Panel C: losartan; Panel D: midazolam; Panel E: omeprazole. Dashed lines represent individual participant data, while the solid line represents the cohort mean

Here, we demonstrate that the mean (±SD) AUC for midazolam at baseline and following a single dose of modafinil were 9.7 ± 3.3 and 9.6 ± 3.8 μg l^{-1} h^{-1}, respectively. In contrast, dosing of modafinil to steady state resulted in a reduction in the mean (±SD) midazolam AUC from 9.7 ± 3.3 to 6.4 ± 2.3 μg l^{-1} h^{-1}. These data demonstrate that when dosed to steady state, but not following a single dose, modafinil may be a perpetrator of mDDIs resulting in a decrease in exposure for co-administered drugs metabolized by CYP3A4. This finding provides direct evidence to substantiate the FDA classification of modafinil as a 'moderate inducer' of CYP3A4 [27], and provides reassurance that co-administration of a single dose of modafinil (i.e. sporadic dosing) with the contraceptive pill is unlikely to place a female at increased risk of unplanned pregnancy.

Following a single modafinil dose, the mean (±SD) AUC for omeprazole increased from 459 ± 161 to 625 ± 228 μg l^{-1} h^{-1}, while dosing of modafinil to steady state resulted in an increase in the mean (±SD) omeprazole AUC from 459 ± 161 to 812 ± 147 μg l^{-1} h^{-1}. These observations are consistent with clinically relevant reversible competitive inhibition of CYP2C19 by modafinil warranting classification of this drug as a borderline moderate inhibitor of CYP2C19. Considering the role of modafinil as an adjunct treatment for depression [28, 29], these data indicate a need for caution and monitoring of potential toxic effects

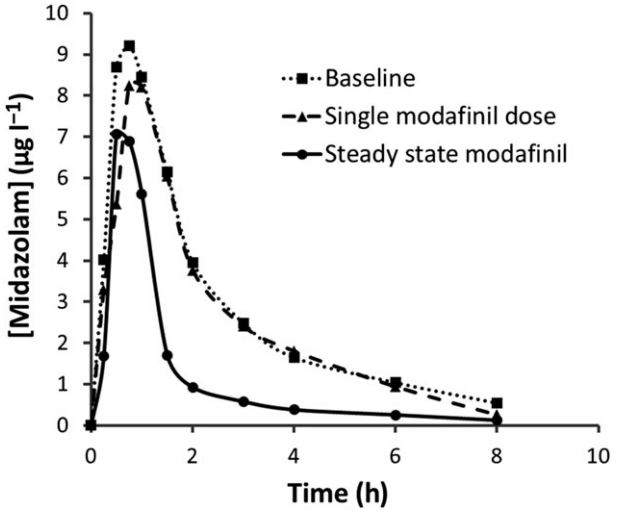

Figure 3
Representative midazolam concentration–time curves (P01) in the absence of modafinil (dotted line with squares), following a single modafinil dose (broken line with triangles) and following steady state dosing of modafinil (solid line with circles)

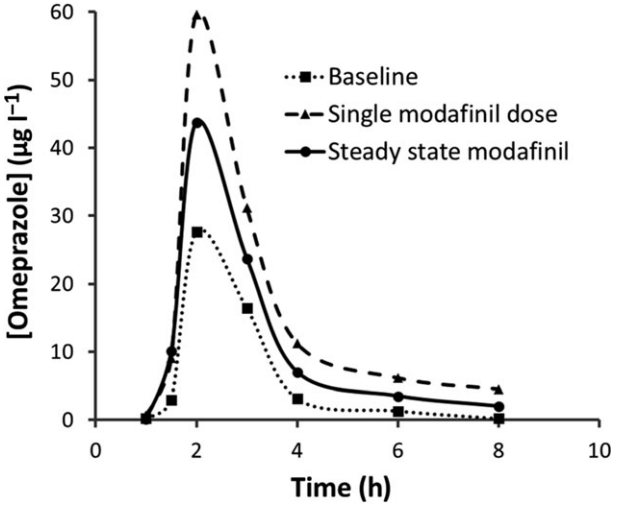

Figure 4
Representative omeprazole concentration–time curves (P01) in the absence of modafinil (dotted line with squares), following a single modafinil dose (broken line with triangles) and following steady state dosing of modafinil (solid line with circles)

(e.g. serotonin syndrome) when modafinil is co-administered with anti-depressant medications that are cleared by CYP2C19, which include the commonly prescribed agents citalopram and sertraline.

Based on the mean Day 8/Day 0 AUC ratio (0.78), there was a trend towards weak induction of CYP2D6 following dosing of modafinil to steady-state; however, the 95% CI for this ratio (0.69–0.88) was contained within the range 0.85–1.2. Similarly, there was no definitive evidence of a change for the secondary parameter ratios (C_{max} or $t_{1/2}$). As such, the current study did not definitively demonstrate the capacity for modafinil to be a perpetrator of MDDIs for this CYP.

In addition to elucidating important clinical findings regarding the magnitude and time course of potential changes in CYP2C19 and CYP3A4 activities caused by modafinil, this is also one of the first reports of a model-informed drug interaction trial performed in an academic institution. Specifically, minimal sample size, and optimal cocktail and perpetrator (modafinil) dosing protocols were established by PBPK modelling using the Simcyp Simulator (Version 15.1) [2]. The use of PBPK modelling informed an efficient and robust trial design to simultaneously evaluate the impact of modafinil on the activity of the five CYP enzymes of key importance in clinical practice.

In conclusion, these data support consideration of the risk of clinically relevant mDDIs when co-administering modafinil with drugs that are primarily cleared by CYP2C19 (single modafinil dose or steady state modafinil dosing) or CYP3A4 (steady state modafinil dosing only) catalysed metabolic pathways. Sporadic recreational dosing of modafinil in young females is unlikely to reduce exposure to the contraceptive pill or increase the risk of unplanned pregnancy. However, co-administration of modafinil with anti-depressant medications that are cleared by CYP2C19 requires careful consideration and monitoring.

Competing Interests

There are no competing interests to declare.

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Contributors

Ag.R., M.J.S. and Ad.R. participated in the research design. Ag.R. and M.V.D. recruited and screened the trial participants. Ag.R., D.W. and A.A.M. were responsible for medical oversight and running the clinical trial. M.V.D. and Ad.R. performed the sample analysis. M.J.S. and Ad.R. performed the data analysis. Ag.R., A.A.M., M.J.S. and Ad.R. wrote or contributed to the writing of the manuscript.

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